

# SELECTING A SYSTEMIC CORTICOSTEROID FOR ACUTE ASTHMA IN YOUNG CHILDREN

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Oral corticosteroids are as effective as intravenous therapy for treating acute exacerbations of asthma. They are available in tablets that can be crushed and mixed with soft food or syrup, and in a variety of liquid formulations that differ in volume required, palatability, patient acceptance, and cost. The most important consideration in product selection for a young child is that the doses can be easily swallowed and retained. (*J Pediatr* 2003;142:S40-S44)

**T**he National Asthma Education and Prevention Program recommends systemic corticosteroids for exacerbations of asthma that are incompletely responsive to therapy with an inhaled  $\beta_2$ -selective sympathomimetic.<sup>1</sup> Systemic corticosteroids are also used to reverse moderate-to-severe airflow obstruction in patients who are relatively asymptomatic, and as a method of confirming the diagnosis of asthma.

Systemic corticosteroids are prescribed for home management, during an unscheduled physician visit, in the emergency department (ED), during hospitalization, and after discharge. There are several drugs from which to choose; they can be administered by different routes, and they are available in a variety of formulations.

The purpose of this article is to review the factors that should be considered by an individual prescriber when selecting a systemic corticosteroid for a young child, and to provide pharmacists and formulary committees with information necessary to select products that increase patients' acceptance of those products.

## SELECTION OF ROUTE OF ADMINISTRATION

Several studies in adults<sup>2-4</sup> and one in children<sup>5</sup> indicate that oral corticosteroids are as effective as those administered parenterally. Becker et al<sup>5</sup> compared oral prednisone with intravenous methylprednisolone in 66 children (40% <6 years of age) hospitalized for acute asthma. The study was a randomized, double-blind, double-dummy design. Patients received either 2 mg/kg prednisone as whole tablets or as crushed tablets mixed with chocolate syrup or applesauce given twice per day and placebo intravenously every 6 hours, or placebo tablets twice per day and 1 mg/kg of intravenous (IV) methylprednisolone every 6 hours. There were no significant differences between groups in length of hospital stay, time required to wean nebulized bronchodilators to an every-6-hours schedule, or peak expiratory flow in those able to perform this maneuver. Supplemental oxygen was required for a significantly shorter period in the prednisone-treated group (mean, 30 hours compared with 52 hours in the methylprednisolone group), and the authors estimated that the cost in their hospital was 10 times higher for IV than oral therapy.

Thus, the oral route is the most convenient and least expensive method of administering systemic corticosteroids, as long as the doses are accepted and retained by the patient. If they are not, IV administration is required in patients treated in the hospital.<sup>1</sup> In ambulatory young children, an intramuscular (IM) injection of a repositi-

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ED	Emergency department
IM	Intramuscular
IV	Intravenous

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**Table. Commercially available oral corticosteroids suitable for treatment of acute asthma in young children\***

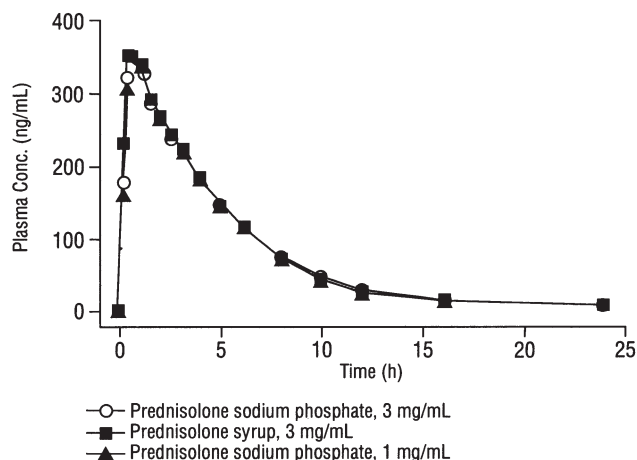
Drug	Dosage form <sup>†</sup>	Strength (s)	Brand name	Manufacturer	Comments
<b>Dexamethasone</b>	Elixir-USP	0.1 mg/mL	Decadron®	Merck	5% alcohol
			Generic	Various	5% alcohol
	Solution	0.1 mg/mL	Generic	Roxane	
	Solution concentrate	1.0 mg/mL	Dexamethasone Intensol™	Roxane	30% alcohol
	Tablets-USP	0.25, 0.5, 0.75, 1.5, 4, 6 mg	Decadron®	Merck	
			Generic	Various	Some generic tablets are not rated therapeutically equivalent to Decadron by the FDA <sup>†</sup>
<b>Methylprednisolone</b>	Tablets-USP	2, 4, 8, 16, 24, 32 mg	Medrol®	Pharmacia and Upjohn	
		All strengths except 2 mg	Generic	Various	
<b>Prednisolone</b>					
	Base				
	Syrup-USP	3 mg/mL, or 1 mg/mL	Prelone®	Muro	5% alcohol
			Generic	Teva, Others	
	Tablets-USP	1, 2.5, 5 mg	Generic	Various	Some generic tablets are not rated therapeutically equivalent by the FDA <sup>†</sup>
<b>Sodium Phosphate Ester</b>					
	Solution-USP	Eq to 1 mg/mL base	Pediapred®	Celltech	392 mg/mL sorbitol
			Generic	Morton Grove	
	Solution	Eq to 3 mg/mL base	Orapred®	Ascent	38 mg/mL sorbitol; store in refrigerator
<b>Prednisone</b>	Solution-USP	1 mg/mL	Generic	Roxane	5% alcohol
	Solution concentrate	5 mg/mL	Prednisone Intensol™	Roxane	30% alcohol
	Tablets-USP	1, 2.5, 5, 10, 20, 50 mg	Deltasone®	Pharmacia and Upjohn	
			Generic	Various	Some generic tablets are not rated therapeutically equivalent to Deltasone by the FDA <sup>†</sup>

\*Products listed in FDA Approved Drug Products with Therapeutic Equivalence Evaluations, Electronic Orange Book, May 2002, <http://www.fda.gov/cder/ob/default.htm>.

<sup>†</sup>USP, Formulation listed in, and meeting drug standards set by, the United States Pharmacopeia, USP25-NF 20, 2002.

tory corticosteroid may be required if oral therapy is not accepted. In an open randomized study, Gries et al<sup>6</sup> reported that a single injection of dexamethasone acetate, a repository slow-release dosage form, was as effective as 5 days of oral prednisolone in relieving an exacerbation of asthma in young children. However, this formulation has been taken off the market. In its place, we use methylprednisolone acetate<sup>7</sup> (Depo-Medrol, Pharmacia and Upjohn, Peapack, NJ) 10 mg/kg as a one-time IM injection (divided into two injection sites, if necessary) when oral therapy

is not tolerated or when adherence to an oral regimen is a concern. In our experience, systemic side effects, such as weight gain and increased acne in teenagers, are more common with repository IM corticosteroids than a 5-day course of oral therapy. This may be a result of the longer duration of action of the repository formulation; the relative insolubility of the acetate ester results in slow dissolution of drug in the muscle and, therefore, slow absorption into the systemic circulation. Although children often have an aversion to injections, Gries et al<sup>6</sup> reported that



**Fig 1.** The mean prednisolone plasma concentrations measured in 23 healthy adults after equivalent doses of 3 different liquid formulations. Each subject received, in random order and taken in a fasting state, a single dose, equivalent to 15-mg prednisolone base, of prednisolone sodium phosphate solution, 3 mg/mL, as Orapred 5 mL (○); prednisolone syrup, 3 mg/mL, as Prelone 5 mL (■); and prednisolone sodium phosphate solution, 1 mg/mL, as Pediapred 15 mL (▲) with a 7-day washout between treatments. There were no significant differences in areas under the curves, peak concentrations, or times to reach the peaks, indicating that the 3 formulations are bioequivalent.

Reproduced with permission from Excerpta Medica, Inc: Ahmed M, Morrel EM, Clemente E. Bioavailability and pharmacokinetics of a new liquid prednisolone formulation in comparison with two commercially available liquid prednisolone products. *Curr Ther Res Clin Exp* 2001;62:548-56.

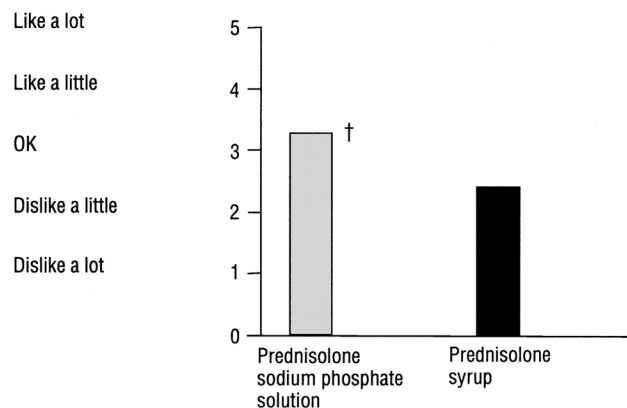
many parents actually preferred this route to the struggle of providing oral medication to their child for 5 days.

## DRUG SELECTION

Dexamethasone, methylprednisolone, prednisolone, and prednisone have all been used to treat acute exacerbations of asthma, although prednisolone and prednisone are more commonly prescribed. Prednisone is an inactive prodrug that undergoes oxidative metabolism in the liver, catalyzed by 11 $\beta$ -hydroxy steroid dehydrogenase to prednisolone, the active drug. Three percent of prednisolone is converted back to prednisone by the same enzyme that is also responsible for the interconversion of hydrocortisone and cortisone. In the absence of severe liver disease, which might prevent conversion of the prodrug to the active form, no benefit is derived from choosing prednisolone over prednisone.

In rabbits, methylprednisolone reaches higher concentrations in bronchoalveolar lavage fluid than prednisolone,<sup>8</sup> suggesting that it might have a therapeutic advantage. However, in the study conducted by Becker et al,<sup>5</sup> methylprednisolone was no more effective than the same total daily dose of prednisone.

Dexamethasone has a greater affinity for the glucocorticoid receptor than methylprednisolone, prednisolone, or prednisone; it is about 5 times more potent when receptor affinity and pharmacokinetics are considered together.<sup>9</sup> Its biologic half-life (ie, the time required for the systemic effects to decrease by 50%) is longer than that of prednisolone and



**Fig 2.** Mean taste scores among 50 children given 2 mL (equivalent to 6 mg of prednisolone base) of prednisolone sodium phosphate solution as Orapred (shaded box) and prednisolone syrup as Prelone (■). Treatments were administered in a randomized, double-blind manner on the same day. There were 5 minutes between treatments during which subjects ate an unsalted cracker. Taste was scored on a scale of 1 to 5 (y-axis) after each treatment. The mean taste score was significantly better for prednisolone sodium phosphate solution ( $\dagger P < .05$ ). Adapted from: Ascent Pediatrics. A blinded randomized balanced block design panel: comparison taste evaluation of Orapred® and Prelone® medication in children. Protocol # PSP-10, March 1999. (Data on file at Ascent Pediatrics, Inc.).

methylprednisolone. This probably is more a function of greater receptor affinity than pharmacokinetics, because the rate of dexamethasone metabolism is only slightly slower.<sup>9</sup>

In a recent open randomized study of 533 children requiring treatment for acute asthma in an emergency department (ED), Qureshi et al<sup>10</sup> concluded that two doses of dexamethasone, one given in the ED and the second given the next day, were as effective as 5 doses of prednisolone given first in the ED and then once daily for 4 days. There were no significant differences in hospital admission rates, relapse rates after discharge from the ED, or symptom persistence. However, the number of patients excluded because of vomiting in the ED, parent nonadherence, and missed days of school were significantly higher in the prednisolone-treated patients. Although the authors attributed the difference to the longer biologic half-life of dexamethasone, it is also possible that other factors contributed to their findings. For example, the higher frequency of vomiting in the ED may have related to the 5% alcohol in the prednisolone syrup, whereas dexamethasone was administered as crushed tablets mixed with soft food or chocolate syrup. The second dexamethasone dose was dispensed directly to parents before they left the ED; with the prednisolone regimen, parents had to fill a prescription for the remaining doses. Furthermore, a larger number of parents may have kept their children home from school in the prednisolone-treated group because they were still taking medication. Last, the study was not double-blinded. It is worth noting that two doses of prednisolone, given as crushed tablets mixed with food or syrup, may have been just as effective as the dexamethasone, but this regimen was not tested.

Although the results of the study by Qureshi et al<sup>10</sup> are intriguing, there is insufficient evidence to conclude that one

corticosteroid is more effective than another when given in equipotent doses.

## ORAL DOSAGE FORMS

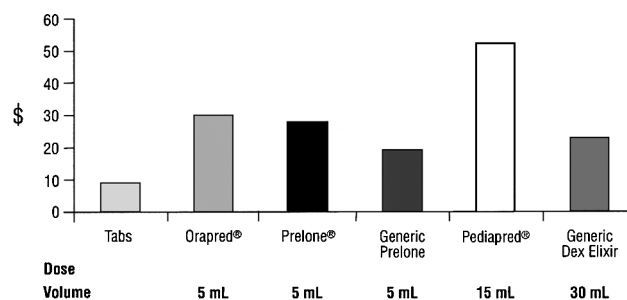
Systemic corticosteroids are available in a variety of oral dosage forms suitable for administration in young children (Table). They differ in strength (thereby affecting the volume or number of tablets that must be administered for a given dose), palatability, patient acceptability, and cost. Tablets can be swallowed whole or, as described above, crushed and mixed with soft foods, such as applesauce or chocolate syrup, to mask the bitter taste. However, parents often prefer liquid formulations.

The volume of liquid required for a given dose is an important consideration because it can affect a child's acceptance of the medication. For example, the dose volume required to deliver 15 mg of prednisolone (1 mg/kg for a 15-kg, average 3-year-old) is 5 mL for the 3mg/mL prednisolone syrup (Prelone, Muro, Tewksbury, Mass) or the 3 mg/mL prednisolone sodium phosphate solution (Orapred, Ascent Pediatrics, Scottsdale, Ariz), 15 mL for the 1-mg/mL prednisolone sodium phosphate solution (Pediapred, Celltech, Rochester, NY), and 30 mL for the equivalent dose (3 mg) of the 0.1 mg/mL-dexamethasone elixir (Decadron Elixir). The strength of the liquid is determined, in part, by the drug's solubility. Some manufacturers have formulated their products with the sodium phosphate ester of prednisolone, which has the greatest solubility, whereas others have added 5% to 30% alcohol, which increases solubility but decreases palatability (Table). The Pediapred formulation of prednisolone sodium phosphate contains 392 mg/mL sorbitol as a sweetener. If 15 mL of this formulation is given to deliver a 15-mg dose of prednisolone base, a 15-kg child would receive 5.88 g (0.4 g/kg) of sorbitol, which is similar to the amount recommended as a potent cathartic for oral decontamination in the treatment of some poisonings and overdoses (ie, 0.5 g/kg). In contrast, the Orapred formulation of prednisolone sodium phosphate contains only 38 mg/mL of sorbitol. If 5 mL of that formulation is given to deliver a 15-mg dose, a 15-kg child would receive .190 g sorbitol (0.01 g/kg), which is considerably less than the cathartic dose.

## BIOAVAILABILITY

Oral absorption of dexamethasone, methylprednisolone, prednisolone, and prednisone is rapid and nearly complete.<sup>11</sup> However, treatment failures have been reported in association with prednisone tablets that dissolved incompletely in vitro.<sup>12,13</sup> Thus, dissolution of the formulation in the gastrointestinal tract appears to be the rate-limiting step in absorption. Prescribers should be aware that several generic tablet products are not approved by the Food and Drug Administration as therapeutically equivalent to their brand name counterparts (Table). Pharmacists should not dispense such products. On the other hand, corticosteroids that are already in solution form are unlikely to have bioavailability problems unless the drug is not stable in its formulation.

Ahmed et al<sup>14</sup> compared the relative oral bioavailability of 3 liquid formulations in 23 healthy adults in an unblinded crossover study with a 7-day washout between treatments. Se-



**Fig 3.** The cost (y-axis) to fill a prescription at a national chain pharmacy located in Gainesville, Florida, with 6 different oral corticosteroid products. Cost was based on dispensing a 5-day supply of 15 mg twice per day (2 mg/kg/day) for prednisone and prednisolone, and 3 mg twice per day (0.4 mg/kg/day) for dexamethasone elixir, for a 15-kg average 3-year-old child. The volume of liquid required for each dose is listed on the x-axis under the product name.

rial blood samples were collected for 24 hours after a single 15-mg dose of the prednisolone sodium phosphate solutions (Pediapred 15 mL of 1 mg/mL base and Orapred 5 mL of 3 mg/mL base) and prednisolone syrup 5 mL of 3 mg/mL containing 5% alcohol (Prelone). Study subjects took each test dose in a fasting state, and plasma concentrations were measured by a validated liquid chromatography/tandem mass spectrometry assay. The areas under the plasma concentration-time curves, which are directly proportional to the amount of drug reaching the systemic circulation, the peak plasma concentrations, and the times to reach the peaks were not significantly different, indicating that the 3 formulations are bioequivalent (Fig 1). Absorption was rapid, reaching a peak concentration in an average of 40 to 50 minutes.

There is no information on the oral bioavailability of these products in patients with liver disease or gastrointestinal tract abnormalities. However, in the absence of these conditions, bioavailability is unlikely to be a clinical problem in children with asthma, as long as the pharmacist dispenses a bioequivalent product.

## PALATABILITY

Perhaps the most important consideration in selecting an oral corticosteroid product for a young child is palatability. Poor taste or a large volume is likely to increase a patient's refusal to swallow doses, thus creating a struggle for the parents. These factors may also contribute to vomiting of medication. As alluded to earlier, Qureshi et al<sup>10</sup> reported that 10 times as many children were withdrawn from their study in the prednisolone-treated group compared with the dexamethasone-treated group because the children vomited two doses during treatment in the ED. Many of the prednisolone-treated patients were taking the syrup containing 5% alcohol, whereas dexamethasone was administered as crushed tablets mixed with soft food or chocolate syrup. This problem of poor acceptance and retention of the oral corticosteroid was also the rationale expressed by Gries et al for their study of an injection of a repository corticosteroid as an alternative.<sup>6</sup>

There are few data on the palatability of oral corticosteroids. The manufacturer of a 3-mg/mL prednisolone sodium phosphate solution (Orapred) commissioned a commercial research company to compare the taste of their product with a 3-mg/mL prednisolone syrup containing 5% alcohol (Prelone).<sup>15</sup> The study was conducted in 50 children, 25 in the group 4 to 7 years of age and 25 in the group 8 to 11 years of age, in a randomized, double-blind, crossover manner. Each subject took 2 mL (6 mg) of one product, ate an unsalted cracker, and then took the second product 5 minutes later. Graded taste responses and product preferences were measured after each product. The mean taste scores were slightly but significantly better after the prednisolone sodium phosphate formulation (Fig 2), and 70% of children indicated a preference for that preparation, which correlated with younger age but not sex. However, the statistical analysis revealed a treatment-sequence bias, with higher taste scores and greater preference for prednisolone sodium phosphate when it was taken first. This makes interpretation of the results difficult. Another study administering a larger dose volume of each formulation on a different day in a crossover manner, or using more subjects with a parallel treatment design on the same day, may be more definitive.

## COST

Cost is the most ambiguous factor in product selection. It depends not only on which product is selected, but also, on who is paying for it. To complicate matters, a product with a lower published manufacturer's cost (the average wholesale price) may not be covered on a state's Medicaid formulary or may not be on a managed care organization's preferred drug formulary. Unless the pharmacist calls the prescriber to change the prescription, a Medicaid patient may not be able to obtain the prescribed medication, or a managed-care patient may have a higher out-of-pocket copay.

Recognizing that there are many answers to the question, "How much does a 5-day course of oral therapy cost?", we determined what a national chain pharmacy serving Gainesville, Florida, would charge those who have to pay the full cost out-of-pocket. A University of Florida pharmacy student, working part time for the chain, entered 6 prescriptions into the store's computer to determine the cost. The selected dose was 15 mg twice per day for 5 days (2 mg/kg/day for a 15-kg, 3-year-old child), except for dexamethasone syrup, which was 3 mg twice per day (0.4 mg/kg/day). Generic prednisone tablets were the least expensive, and the 1 mg/mL prednisolone sodium phosphate solution (Pediapred) was the most expensive because it is

more dilute and requires a larger volume to deliver 15 mg (Fig 3). It is noteworthy that the dose volume (listed on the *x*-axis of Fig 3) would make dexamethasone elixir a very impractical choice.

## CONCLUSION

In selecting an oral corticosteroid for a young child, the most important factors to consider are whether a parent can obtain the prescription (ie, they can afford it or the product is covered on the formulary), and whether the child will swallow and retain the doses.

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